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IN THE U.S. PATENT AND TRADEMARK OFFICE

Inventor Maria GAZDAG et al
Patent App. 10/564,017
Filed 15 May 2006 Conf. No. 3986
For PROCESS FOR THE PREPARATION OF CHIRALLY PURE N-
 (TRANS-4-IS

Art Unit 1621 Examiner Puttlitz, K
Hon. Commissioner of Patents
Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 CFR 1.132

I, Maria GAZDAG, a citizen of Hungary, residing at Olt u.
34, Budapest, Hungary, declare as follows:

THAT I have a number of years of experience in both the
synthesis and spectral analysis of organic compounds;

THAT my full curriculum vitae may be attached hereto;

THAT I am an Applicant in US Patent Application Serial
No. 10/564,017 filed 15 May 2006 and directed to A PROCESS FOR THE
PREPARATION OF CHIRALLY PURE N-(TRANS-4-ISOPROPYL-
CYCLOHEXYLCARBONYL)-D-PHENYL-ALANINE AND CRYSTALLINE MODIFICATIONS
THEREOF;

THAT I am aware that the Examiner in US Patent Application Serial No. 10/564,017 has questioned whether the compound according to the present invention, which is designated as nateglinide crystalline modification "G" hereinafter Form G (Richter) is really a different crystalline form of nateglinide from nateglinide crystalline modification "G" hereinafter Form G (Teva) disclosed in US Patent Application 2004/0181089;

THAT in order to establish that nateglinide Form G (Richter) is a different crystal from nateglinide Form G (Teva), I either have directly conducted or supervised the carrying out of the following tests:

TESTS

Hereinafter the following notation will be used: Form G of Nateglinide disclosed in US Patent Application Serial No. 10/564,017 (published US Patent Application 2007/0043117) is referred to as Form G (Richter), and Form G of Nateglinide disclosed in published US Patent Application US 2004/0181089 to TEVA is referred to as Form G (Teva).

In order to prove that Form G (Richter) and Form G (Teva) are two distinct solid forms of the substance we prepared Form G

(Teva) by following the general procedure described in published US Patent Application 2004/0181089 according to Paragraphs [0226]-[0231]), especially Paragraph [0231], and measured the solid state characteristics of the obtained crystals (bn.: VI-285/4). Form G (Teva) was crystallized from 2-propanol/water=60/40% (v/v) solution by cooling (bn.: VI-285/4), and was identified by X-ray powder diffraction measurement (see XRPD patterns below).

It can be seen that the diffractogram of the obtained crystalline material (attached Spectrogram B) is nearly identical to that of Form G (Teva) having a diffractogram according to Figure 6 of US Patent Application 2004/0181089 (attached Spectrogram A). Any observable slight differences between the two versions of the Form G (Teva) may originate from the different level of crystal perfection of the samples and different resolution of the diffractometers used. Reflection at about $3.6^{\circ} 2\theta$ on the pattern of Form G (Teva) may relate to some polymorphic impurity as it can be seen also on the patterns of other solid forms of US Patent Application US 2004/0181089. Nevertheless, based on XRPD results, the crystal form of the reproduced material (bn.: VI-285/4) is clearly identical to Form G (Teva).

The Table below shows characteristic vibrational bands (IR and Raman) of Form G (Richter) as disclosed in the present application and in our published US Patent Application

2007/0043117, and Form G (Teva) measured on the sample (bn.: VI-285/4) that we reproduced according to published US Patent Application 2004/0181089. Spectrogram C as attached is the same as the spectrogram in Figure 1 of the present application and is a Raman spectrogram of Form G (Richter) according to the present invention. Spectrogram D as attached is a Raman spectrogram of Form G (Teva) that we reproduced according to the procedure in US Patent Application 2004/0181089. Spectrogram E as attached is the same as the spectrogram that is in Figure 2 of the present application and is an IR spectrogram of Form G (Richter) according to the present invention. Spectrogram F as attached is an IR spectrogram of Form G (Teva) that we reproduced according to the procedure in US Patent Application 2004/0181089. It is clearly seen that many vibrational bands of the two solid forms occur at different wave numbers. Differences exceeding the $\pm 4 \text{ cm}^{-1}$ uncertainty of the method are underlined, unique bands of Form G (Richter) and that of Form G (Teva) are typed bold face. It can be seen that characteristic peaks of Form G (Richter) are either not present in Form G (Teva) (bn: VI-285/4) or appear at wave numbers exceeding the generally accepted uncertainty limit of the method. Other spectral differences, including band shape and relative intensities, can be seen on the comparison of full IR and Raman spectra of the two forms below.

Characteristic IR and Raman absorption bands of two different solid forms of Nateglinide

IR [cm ⁻¹]	
Form G (Richter)	Form G (Teva)
US 2007/0043117	VI-285/4
3313	<u>3303</u>
3064	3065
3031	3031
2934	2936
2856	<u>2848</u>
1763	<u>1725</u>
1735	<u>1718</u>
1648	1648
1614	np
1533	<u>1542</u>
1448	1446
1386	1385
1368	1367
1216	1214
1180	<u>1186</u>
1113	<u>1120</u>
1081	1080
934	935
750	<u>758</u>
700	700
574	574
491	<u>498</u>

Raman [cm ⁻¹]	
Form G (Richter)	Form G (Teva)
US 2007/0043117	VI-285/4
3057	3059
2938	2940
2868	2867
np	<u>2844</u>
1762	np
1710	np
1651	1650
1606	1606
1586	1587
1462	1462
1442	1442
1339	1338
1207	1209
1182	1183
1158	1157
1085	1082
1004	1004
949	951
885	884
822	<u>818</u>
793	794

THAT based upon the data presented above, I conclude the following:

THAT Form G (Richter) crystal modification of nateglinide has a Raman spectrum with intensive bands at 1762, 1710, 1182 and 822 cm^{-1} and that Form G (Teva) crystal modification of nateglinide has a Raman spectrum with none of these intensive bands;

THAT Form G (Richter) crystal modification of nateglinide has an IR spectrum with intensive bands at 1763, 1735, 1614, 1533, 1180, 750, 574 and 491 cm^{-1} and that Form G (Teva) crystal modification of nateglinide has an IR spectrum with none of these intensive bands;

THAT I further conclude that based on comparison of the IR and Raman spectra, it can be unambiguously stated that Form G (Richter) and Form G (Teva) are two different solid forms of Nateglinide;

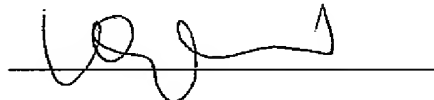
THAT I am aware of no information inconsistent with the information presented above or which would lead one to a contrary conclusion; and

I hereby certify that all statements made herein of my own knowledge are true and that all statements made on information and

belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine, or imprisonment, or both under 18 USC 1001 and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

04 March 2010

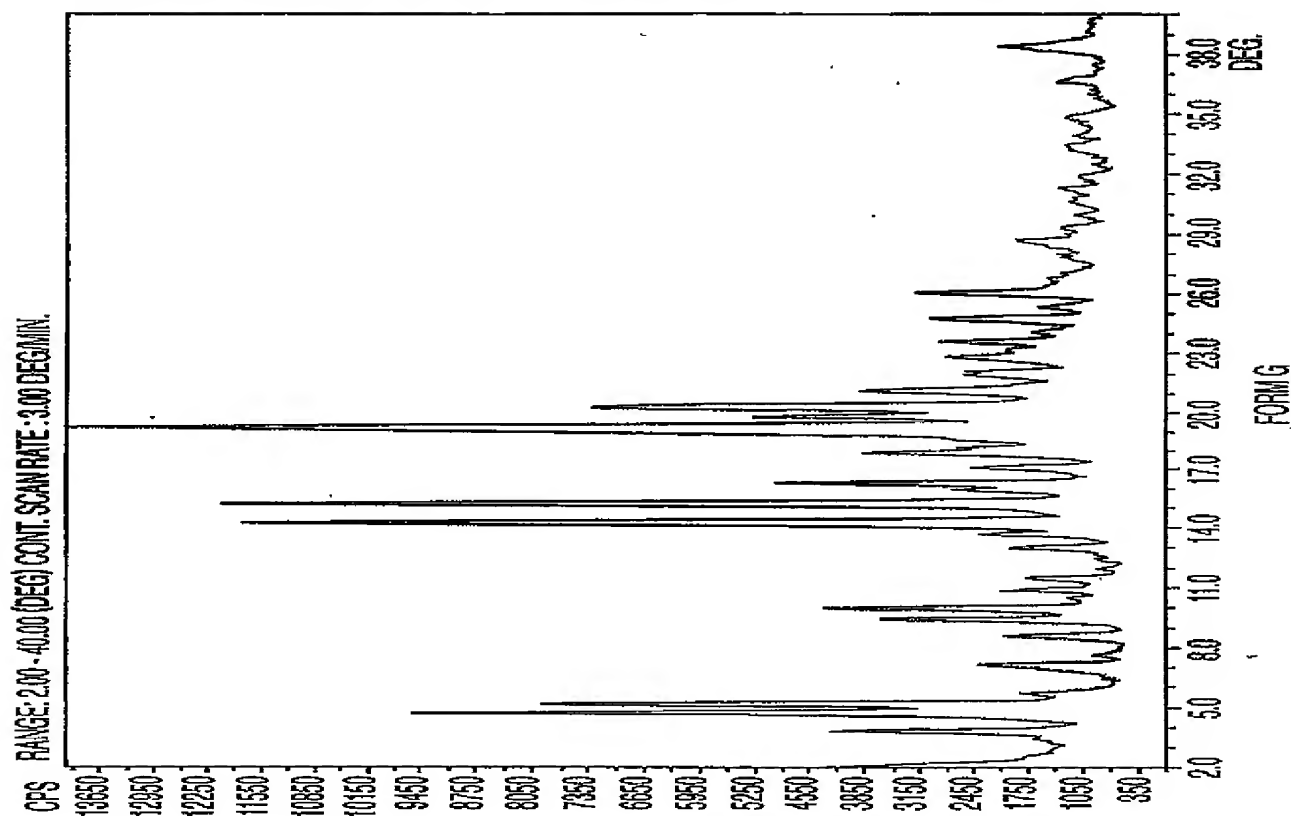
Date

A handwritten signature in black ink, appearing to read 'Maria Gazdag', is written over a horizontal line.

Maria Gazdag

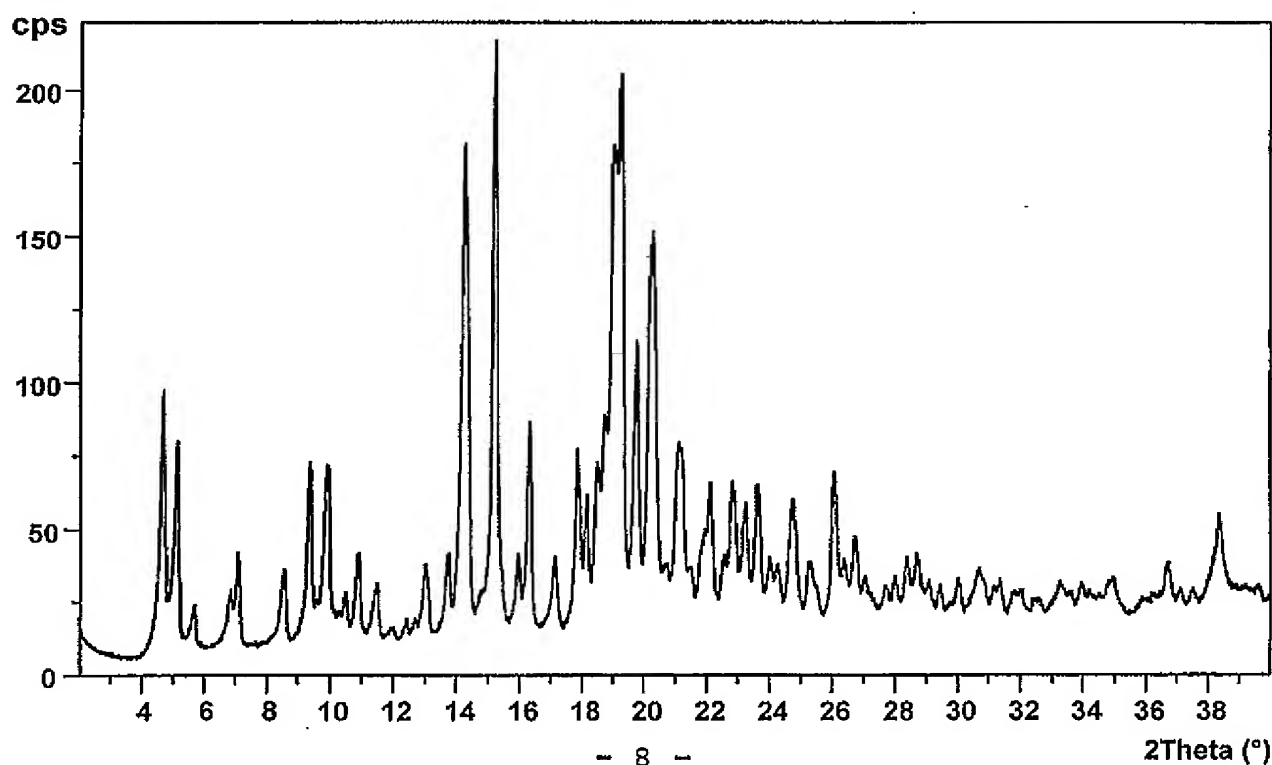
Spectrogram A (Fig. 6 of US 2004/0181089)

XRPD pattern of Nateglinide Form G according to application US 2004/0181089

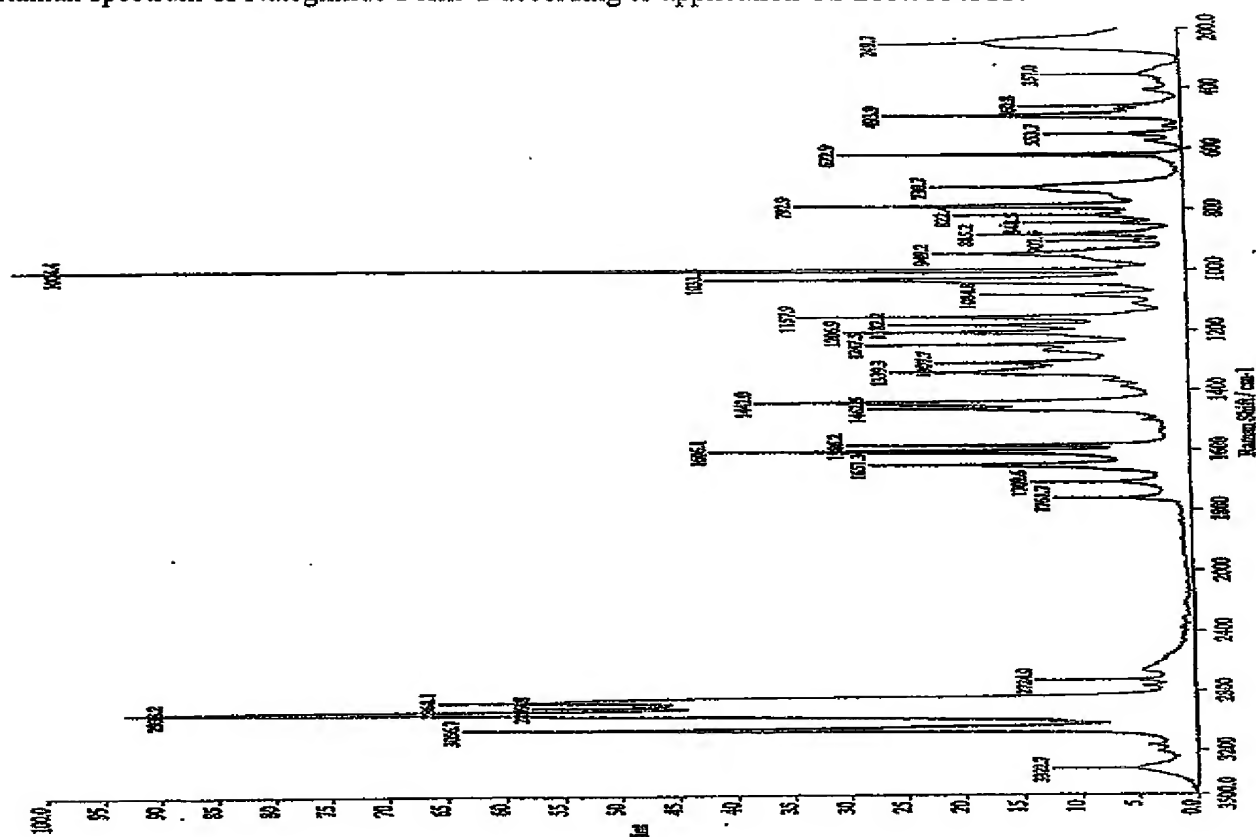


Spectrogram B

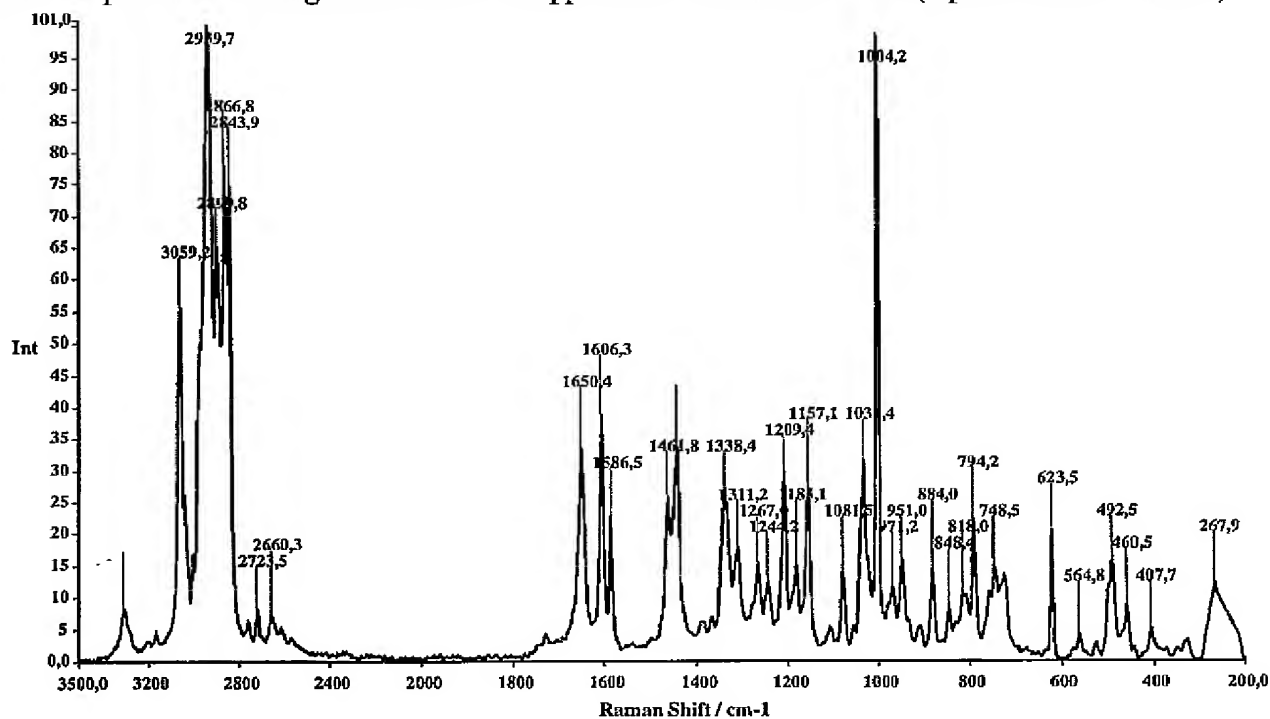
XRPD pattern of Nateglinide Form G of application US 2004/0181089 (reproduced as VI-285/4)



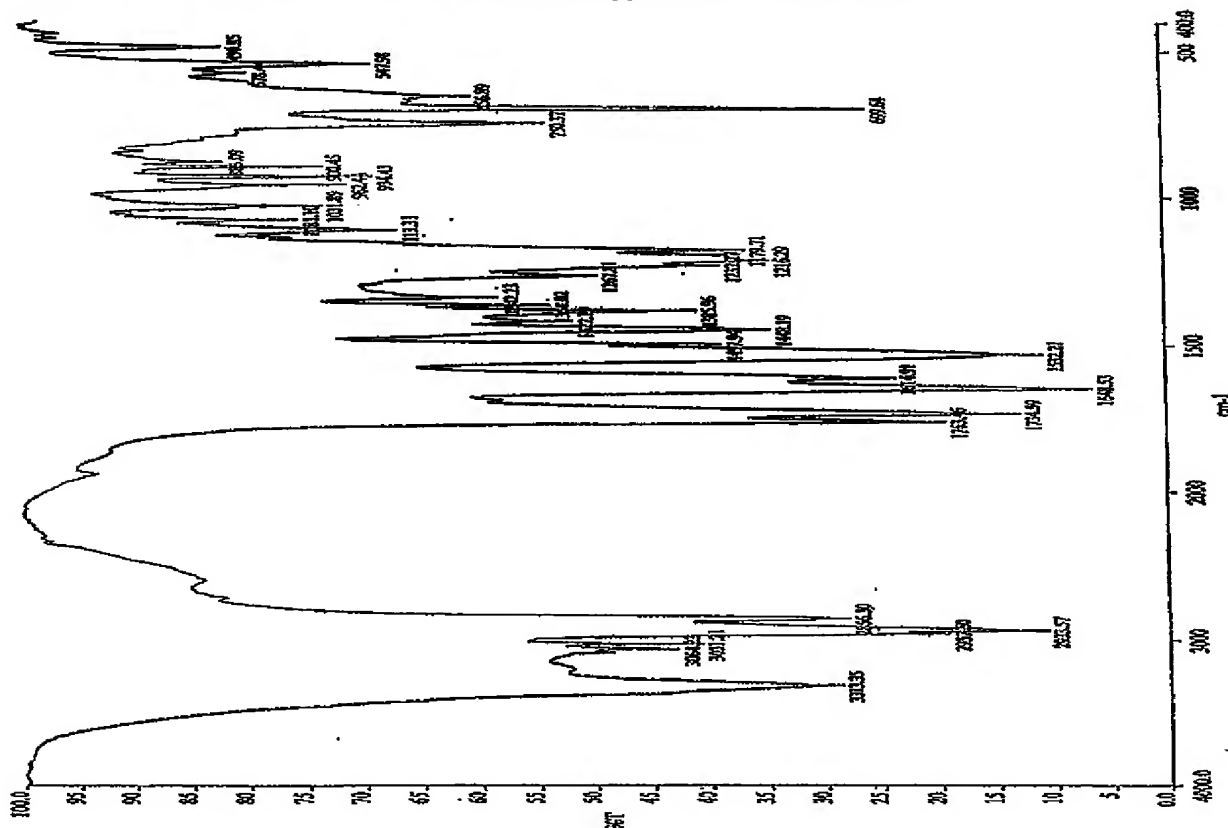
Spectrogram C (Fig. 1 of Ser. No. 10/564,017
Raman spectrum of Nateglidine Form G according to application US 2007/0043117



Spectrogram D
Raman spectrum of Nateglidine Form G of application US 2004/0181089 (reproduced as VI-285/4)



Spectrogram E (Fig. 2 of Ser. No. 10/564,017)
IR spectrum of Nateglinide Form G according to application US 2007/0043117



Spectrogram F
IR spectrum of Nateglinide Form G of application US 2004/0181089 (reproduced as VI-285/4)

